REMARKS

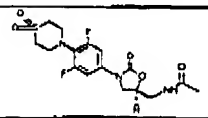
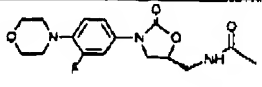
A. Claim Amendments

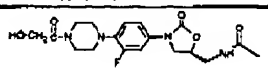
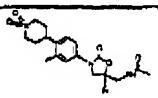
Claims 1, 3-22, and 24-29 are pending in the application, claims 2 and 23 having been canceled in response to a previous Office Action.

Applicants propose to amend claims 1 and 21, as described herein above, to add the term "wherein the oxazolidinone antibacterial drug is no more than sparingly soluble in water" to each claim. Oxazolidinone antibacterial drugs of the formula of claims 1 and 21 are inherently no more than sparingly soluble in water. Some oxazolidinone drugs are only slightly soluble, or even very slightly soluble in water. Each of these descriptive terms relating to solubility is clearly defined by the USP, and understood by those of skill in the art of the present invention. (See solubility table in attached copy of p. 7 of USP XX). Specifically, the term "sparingly soluble" is defined by the USP as referring to a solute that requires from 30 to 100 parts of solvent to be solubilized. It follows that a drug which is only sparingly soluble in water would have a solubility of from 9.9 mg/ml to 32 mg/ml.

Applicants respectfully submit that the amendment of claims 1 and 21 to add the additional solubility term cited immediately above would not add new matter to the present application, as the solubility of the oxazolidinone antibacterial drug element of the present invention in water is an inherent property of the element. As evidence of this inherent property, Applicants present solubility data for four oxazolidinones antibacterial drugs of the formula of claims 1 and 21 in Table I, below.

TABLE 1

Compound	Structure	Solubility in Water (mg/ml)
Oxazolidinone A, Reg. No. 383199-88-0		0.40
Oxazolidinone B (Linezolid)		2.7

Compound	Structure	Solubility in Water (mg/ml)
Oxazolidinone C, Reg.No.383199-88-0		10
Oxazolidinone D, PNU-141659		0.4

The data presented in Table I, above, came from experiments performed by scientists at Pharmacia & Upjohn Company. The data has not been published.

Note that, using the USP standard nomenclature to describe solubility, the oxazolidinone antibacterial drug listed in Table I with the highest solubility, Oxazolidinone C, is only sparingly soluble in water. Linezolid would be considered slightly soluble in water, at about 2.7 mg/ml. The two oxazolidinones with the lowest solubility in water, Oxazolidinones A and D, are only very slightly soluble therein.

For reasons set forth above, Applicants respectfully submit that incorporation of the amendments to claims 1 and 21 proposed herein above would not constitute the addition of new matter to the present application.

B. Status of Previous Grounds of Rejection

Under 37 CFR § 1.113(b), an examiner is required, in any final rejection or action to "repeat or state all grounds of rejection then considered applicable to the claims of the application, clearly stating the reasons in support thereof." (See also, MPEP 706.07).

Several grounds for rejecting claims 1-29 were set forth the previous Office Action on the merits, mailed December 18, 2002. The present Office Action stated that a Declaration under 37 CFR 1.132 filed in response to that Office Action is "insufficient to overcome the rejection of claims 1-29 based upon specific references under 35 USC 102 and 103 as set forth in the last Office action." (Office Action, p. 5, paragraph No. 4) The present Office action goes on to state that arguments set forth in the response to the same Office Action filed with the Declaration "have been considered but are moot in view of the new ground(s) of rejection." (Office Action, p. 5, paragraph No. 5). However, none

of the previous grounds of rejection are repeated in the present Office Action, or otherwise indicated as remaining applicable.

Applicants understand the statement from paragraph No. 5 in the present Office Action, regarding the arguments set forth in response to the previous Office Action being moot, indicate that the previously stated grounds of rejection have been withdrawn, particularly. Specifically, Applicants understand the last statement and the absence of any restatement of the previous rejections with reasons in support thereof, as required under 37 CFR §1.113, to mean that the three rejections of various claims of the present application under 35 U.S.C. §102(b), for anticipation by each of three different references, Maillard (US Pat No. 3,721,675), Borgulya *et al.* (US Pat No. 5,574,055), and Kaplan *et al.* (U.S. Pat. No. 4,727,070) were withdrawn in view of Applicants' amendment and response to the previous Office Action. Applicants similarly understand this last statement, and the absence of statements required under 35 CFR §1.113, to imply that the rejection in the previous Office Action of claims 1-29, under 35 U.S.C. §103(a) over Malliard *et* al, Borgulya *et al.*, and Kaplan *et al.*, in view of Barbachyn *et al.* (U.S. Pat. No. 5,699,792), **Linezolid** (*Drugs of the Future* **1996**, 21(1): 116-1123, XP 000654643) and Miyauchi (U.S. Pat. No. 4,900,730) has also been withdrawn in view of Applicants' response to the previous Office Action on the merits.

C. New Ground for Rejection, Under 35 U.S.C. §103

Claims 1, 3-22, and 24-29 were rejected under 35 U.S.C. §103(a) as being unpatentable over a new combination of three references cited in the previous Office Action, Barbachyn *et al.*, Borgulya *et al.*, Kaplan *et al.*, and Miyauchi.

As was noted in response to the previous Office Action, in order for any claim to be unpatentable over one or more prior art references, under 35 U.S.C. § 103(a):

> "[A]ll the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)." MPEP 2143.03.

1. References Cited Fail to Teach or Suggest Elements of the Invent on

Applicants respectfully submit that at least one element common to all the claims of the present application is neither taught nor suggested by Barbachyn *et al.*, Borgulya *et al.*, Kaplan *et al.*, or Miyauchi *et al.*, or by any combination of the four references.

Barbachyn *et al.* is described in the Final Office Action as disclosing "oxazolidinone antimicrobial compounds having an identical structure to the compounds of the present invention," and for stating that such compounds can be "formulated into capsules, dispersed granules, and similar pharmaceutical dosage forms." (Final Office Action, pp. 2 and 3). It is noted in the Final Office Action, that Barbachyn *et al.* fails to disclose any rectal suppository formulation. However, the Office Action goes on to state that "it would be within the level in the art to modify a capsule for rectal suppository administration."

Rectal suppository capsules, particularly soft suppository-shaped elastic capsules, were known at the time the present invention was made. See, for example, Remington: The Science and Practice of Pharmacy, 20th ed. (pub. by Lippincott Williams & Wilkins, 2000), pp 889 to 890, a copy of which is attached. Such suppository capsules were designed with a "soft, globular, gelatin shell" that could be filled with a carrier medium, such as a liquid or oil, with an active agent dissolved therein. (*Id.*) For a description of one known method of producing liquid-filled soft shell capsules, see Bottom *et al.*, *Journal of Pharmaceutical Sciences* 86(9): 1057-1061 (Sept. 1997), a copy of which is attached.

Applicant submits that, even one of ordinary skill in the art might have been able to make modify the teachings of Barbachyn *et al.* to make a "capsule for rectal suppository administration," as suggested by the Office Action, it would not have been obvious to that individual to make any composition of the present invention, including the rectal capsule of claim 9, or to practice any method of treatment or prevention of the present invention. Even prior to (and after) amendment as proposed herein, the only two independent claims, claims 1 and 21, were directed to or included an element of a "pharmaceutical composition, comprising at least one oxazolidinone antibacterial drug in a solid particulate form dispersed in a pharmaceutically acceptable carrier in which the at

least one oxazolidinone is poorly soluble. . ." (Language common to claims 1 and 21, after amendment; emphasis added.) Applicants respectfully submit that Barbachyn *et al.* fails to teach or suggest any pharmaceutical composition, including any rectal capsule dosage form, wherein an oxazolidinone antibacterial drug is present in a solid particulate form dispersed in a pharmaceutically acceptable carrier in which the at least one oxazolidinone is poorly soluble. Applicants respectfully submit that this particular element of the present invention missing from Borgulya *et al.* cannot be found in any of the other three references cited as basis for this rejection, particularly, when the element is considered after amendment as proposed herein to refer to the inherent properties of solubililty of the oxazolidinone antibacterial drug of claims 1 and 21 in water.

Borgulya *et al.* is cited as disclosing a suppository formulation comprising what the Final Office Action describes as an "oxazolidinone antimicrobial agent" (citing Example A) and formulations of the agent in the form of capsules, dispersed granules, etc. The Final Office Action notes acknowleges that the agent disclosed by Borgulya *et al.* is not one of the same oxazolidinone compounds disclosed by Barbachyn *et al.* The Office Action goes on to state that it would have been obvious to substitute the compound of Barbachyn *et al.* into the composition of Borgulya *et al.* to make the compositions of the present invention.

Borgulya *et al.* teaches a number of different compositions of oxazolidinone derivatives known to be useful in the "prevention of control of depressive, panic and anxiety states, and treatment of certain cognitive disorders and neurodegenerative diseases." (Borgulya *et al.*, Abstract). Example A of Borgulya *et al.* provides a hypothetical example of a suppository of one such derivative, (RS)-3-(4-Cyclohexyl-phenyl_-5-hydroxymethyl-oxazolidin-2-one. However, the Example only describes the suppository in terms of the amount of active ingredient and total suppository mass. No specific information is provided in regarding the composition of the suppository, or regarding the solubility properties of the active agent to be incorporated into the suppository. With such little information provided by Borgulya *et al.* about the one hypothetical suppository disclosed therein, Applicant respectfully submits that Borgulya *et al.* fails to teach or suggest a pharmaceutical composition of any drug in a solid

particulate form dispersed in a pharmaceutically acceptable carrier in which the drug is poorly soluble. The reference also fails to teach or suggest the production of a suppository of any drug which is no more than sparingly soluble in water. Therefore, even if one were to substitute the oxazolidinone antibacterial drug of Barbachyn *et al.* in the compositions of Borgulya *et al.* the two references would not teach or suggest the compositions or methods of the present invention.

The Final Office Action cites Kaplan *et al.* as disclosing a suppository formulation comprising oxazolidinone compounds, where the lipophilic carrier is a hard fat (Example 7). The Final Office Action acknowledges that active agent in Kaplan *et al.* is different from that of the present invention. However, it goes on to state that it would have been obvious to substitute the oxazolidinone antibacterial drugs of Barbachyn *et al.* in the formulation of Kaplan *et al.*. The suppository dosage forms of Example 7 of that reference are described therein as being produced by dissolving a particular antibiotic agent in a hard fat suppository base, and pouring the resulting composition into molds. Like Barbachyn *et al.* and Borgulya *et al.*, Kaplan *et al.* fails to teach or suggest a pharmaceutical composition of any drug in a solid particulate form dispersed in a pharmaceutically acceptable carrier in which the drug is poorly soluble. Like the other two references, Kaplan *et al.* also fails to teach or suggest the production of a suppository of any drug which is no more than sparingly soluble in water. Therefore, Applicants respectfully submit that the pharmaceutical compositions of and methods of the present invention would not have been obvious to one of ordinary skill in the art, even if they were to substitute the oxazolidinone antibacterial drugs of Barbachyn *et al.* in the suppository formulation of Kaplan *et al.*

The final reference cited as basis for the present rejection, Miyauchi, is described in the Final Office Action as disclosing rectal suppositories of antibacterial agents that are "micronized from 1-50 microns, and dissolved in the hard fat Witepsol H-15." Miyauchi teaches that the medicines employed in the formulations disclosed therein are preferably "water-soluble medicines." (Miyauchi, col. 5, lines 26-27). The term "water-soluble" is defined as "a solubility of not more than 30 parts water per one part of substance on the basis of the United States Pharmacoperia." (*Id.*, col. 2, lines 43-46) This definition

clearly takes. As noted in the Amendment remarks section, herein-above, the oxazolidinone antibacterial drug in the compositions and used in the methods of the present invention is no more than "sparingly soluble" in water, on the basis of the same US Pharmacoperia definition standard. In other words, the oxazolidinone antibacterial drug has a solubility of one part drug to more than 30 parts water. This inherent property of the at least one oxazolidinone antibacterial drug of the compositions and method of the present invention is made even more clear upon incorporation of the amendment proposed herein. Miyauchi neither teaches nor suggests that the drug in the micronized particles disclosed in that reference is poorly soluble in the hard fat base used to make the rectal suppositories disclosed therein. Therefore, Miyauchi fails to make up for the deficiencies in the teachings of the other three references cited as basis for this rejection.

2. Missing Elements Not Obvious from General Knowledge of the Art

In order to more clearly emphasize the surprising and unexpected nature of the pharmaceutical compositions and methods of the present invention, Applicants propose to amend the only two independent claims herein by inserting a reference to an inherent property of the oxazolidinone antibacterial drugs of claims 1 and 21, a reference to the fact that those particular drugs are no more than sparingly soluble in water. (proposed amended language underlined). As further evidence of the expectations of one of ordinary skill in the art, Applicants submit The Theory and Practice of Industrial Pharmacy, ed. by Lachman *et al.* 3rd ed., pub. by Lea & Febiger, Philadelphia (1986), pp 564-567. Beginning on p. 566 of that reference is a discussion of the effect of solubility of a drug in a vehicle and in colon fluids on absorption through the rectal mucosa. It specifically teaches that in order for a drug to be absorbed, it "must be released from the suppository and distributed to sites of absorption." (Lackman *et al.* p. 566). That particular reference constitutes evidence that the general knowledge available to one of ordinary skill in the art at the time the present invention was made taught away from any pharmaceutical composition of a drug for rectal administration wherein the drug is present in particulate form in a carrier, and the drug is no more than sparingly soluble in water. For, if a drug is no more than sparingly soluble in water, one would not expect it to go into solution in colon fluids, so that it can be absorbed through the rectal mucosa.

For reasons set forth above, Applicants respectfully traverse the rejection of claims 1, 3-22, and 24-29, under 35 U.S.C. §103(a) as being unpatentable over Barbachyn *et al.*, Borgulya *et al.*, Kaplan *et al.*, and Miyauchi.

SUMMARY

Applicants respectfully request entry of all amendments proposed herein above, as all would place the application in a better position on appeal, should appeal become necessary. For reasons given above, Applicants respectfully submit that all of the claims remaining pending in the present case (i.e., claims 1, 3-22, and 24-29) after amendment as proposed herein, are in condition for allowance. Issuance of all the claims is, therefore, requested. The Examiner is invited to contact the undersigned at the telephone number given below, should he wish to discuss the present amendment and suggest changes to the claims in order to further prosecution of the application.

Dated: Apr. 7, 2004

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